Antifungals Combination in Pediatric Patients with Invasive Fungal Infections: A Systematic Review and Meta-Analysis

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Abstract

Objective: Invasive fungal infections (IFIs) remain a significant cause of morbidity and mortality among children with immunosuppression due to genetic disorders, malnutrition, infection, and cancer chemotherapy. The use of monotherapy antifungals in pediatric IFIs remains the current therapeutic standard. However, studies have shown increased efficacy in combination with antifungals to combat IFIs. Hence, this research focuses on the efficacy and safety of combination antifungal therapy in pediatric IFIs.

Methods: The literature search across PubMed, ScienceDirect, BMJ Journals, ProQuest, and Springer databases yielded 419 articles. A total of 395 articles were filtered, leading to 24 articles assessed for eligibility and overall analysis, which resulted in six included studies for quantitative synthesis. Quality appraisal used RoB 2.0, while meta-analysis used RevMan 5.4.

Results: Our analysis indicated five studies with a low risk of bias and 1 study with a moderate risk. A non-statistically significant overall result favoring the combined group was found in survival rate, complete response rate, and favorable response rates. In contrast, a statistically significant result was found in the overall response rate. For mortality and unfavorable response rates, statistically significant overall results favoring a single/placebo group were found.

Conclusion: Antifungal combination therapy has shown significant efficacy in overall and complete response rates, favoring the combination antifungal therapy.

Keywords: invasive fungal infection, children, combination antifungal therapy, infectious disease, medicine

Introduction

Invasive fungal infections (IFIs) emerge as a prominent contributor to morbidity and mortality in pediatric patients diagnosed with hematological malignancies.[1-3] A broad range of pediatric patients susceptible to IFIs encompasses those undergoing chemotherapy for malignancies, recipients of pediatric hematopoietic stem cell transplantation (HCT) or solid organ transplantation (SOT), children with primary immunodeficiency (PID), individuals receiving immunomodulating therapy for autoimmune conditions, and those with acquired immunodeficiency. In addition to these cohorts, neonates and children admitted to intensive care units (ICUs), children with immunosuppression due to genetic disorders, malnutrition, infection, and cancer chemotherapy also face the risk of developing IFI.[1,4,5] Moreover, updated definitions of IFI and discrepancies in diagnostic criteria contribute to the complexity of evaluating the prevalence of IFI, posing challenges for clinical decision-making.[1,6]

Currently, the available guidelines recommend the implementation of monotherapy for IFI cases among pediatric patients. However, recent findings discovered that the combination of antifungal therapy may intensify the rate of fungal elimination through a synergistic effect, widen the range of antifungal scope, and reduce the possibility of therapy resistance.[7,8] The utilization of antifungal combination therapies in patients with hematologic malignancies is based on considerations of potential benefits, including preventing resistance problems, enhancing treatment efficacy, and reducing side effects.[9,10] Combined antifungal therapy is a concept that has yet to be explored; it has been effectively employed in treating certain well-defined infections.[11] However, the role of combination regimens in treating IFI in patients with hematologic malignancies remains a subject of controversy.[12] Controversies arise regarding the advantages of employing a combination antifungal treatment in this demographic. Precisely, the endeavor to enhance treatment effectiveness is frequently counterbalanced by apprehensions of reduced safety attributed to cumulative toxicities.[13]

Hence, this systematic review and meta-analysis evaluates the efficacy and safety of combination antifungal therapies and addresses the controversies associated with their use in pediatric patients with hematologic malignancies. Through a comprehensive analysis, we aim to contribute valuable insights that can guide clinicians in making informed decisions when choosing antifungal therapy.

Methods

This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis protocol (PRISMA). This study was registered in **PROSPERO** with the registration number **CRD42024503620.**

Study Eligibility Criteria

The Inclusion criteria of the studies were: 1) Observational studies that reported on the application of antifungal combinations and 2) Studies that included pediatric patients (< 18 years old) as the studies' population. After assessing each study to determine its eligibility, we excluded some of the studies due to 1) Observational studies that only reported on the application of single antifungal prophylaxis, 2) non-retrievable/incomplete studies, and 3) non-English literature.

Search Strategy

Two authors (RNR, FAG) went through literature searches from PubMed, ScienceDirect, Cochrane Library, Nature, and BMJ Journal databases. The keywords being used for this study consist of "Antifungal Combination," "Invasive Fungal Infection," or "IFI," and "Pediatric patients." The inclusion criteria of this meta-analysis refer to the patient, intervention, control, outcome, time, and settings (PICOTS) framework in **Table 1**.

Table 1: PICOTS Table.

Population	Paediatric patients < 18 years old
Intervention	Combined Antifungal Therapy
Comparator	Single-antifungal medication or Placebo

Outcome	Overall responses, survival rates, mortality rates
Study Design	Observational studies & RCT

Data Extraction

After analyzing and assessing the studies' eligibilities, two authors (FAG and DDCHR) sectioned all parameters and data. All the disagreements during the process were discussed with the other five authors (RNR, NJ, HY, INK, MAE). Studies that met the inclusion criteria were assessed thoroughly, and those that met the exclusion criteria were excluded. The studies included were further evaluated using quantitative and qualitative synthesis. The authors then examined the characteristics of the studies, the follow-up characteristics, and the risk of bias from all the included studies in this meta-analysis.

Qualitative Synthesis

The risk of bias in included studies was assessed using the Risk of Bias in Non-randomised Studies - of Interventions (ROBINS-I). Afterward, the results were inputted into the "bias" section of the spreadsheet. The spreadsheet was then uploaded to the ROBVIS website to display the assessment result using the traffic light system.

Quantitative Synthesis

Review Manager 5.4 software (Cochrane Collaboration, Oxford, UK) was used for the meta-analysis. Clinical outcomes from continuous data were reported as mean difference (MD) and 95% confidence interval (CI) and presented using a forest plot. The I^2 method was used to calculate statistical heterogeneity (25% was considered low heterogeneity, 25-50% moderate heterogeneity, and >50% high heterogeneity). A random effect model was used to conduct additional analysis when the meta-analysis revealed significant heterogeneity. I^2 >50% was considered significantly heterogeneous, while $P < 0.05$ was statistically significant.

Results

Study Selection and Identification

Following the elimination of duplicate studies and abstract screening based on inclusion and exclusion criteria from several databases, such as PubMed, ScienceDirect, Cochrane Library, Nature, and BMJ, a total of 15 full-text studies underwent comprehensive examination, with seven clinical trials were chosen for this review, as depicted in **Figure 1**. The studies were assessed, and different outcomes were revealed to determine the combination of antifungal therapy compared to monotherapy in terms of overall responses, survival rates, and mortality rate parameters.

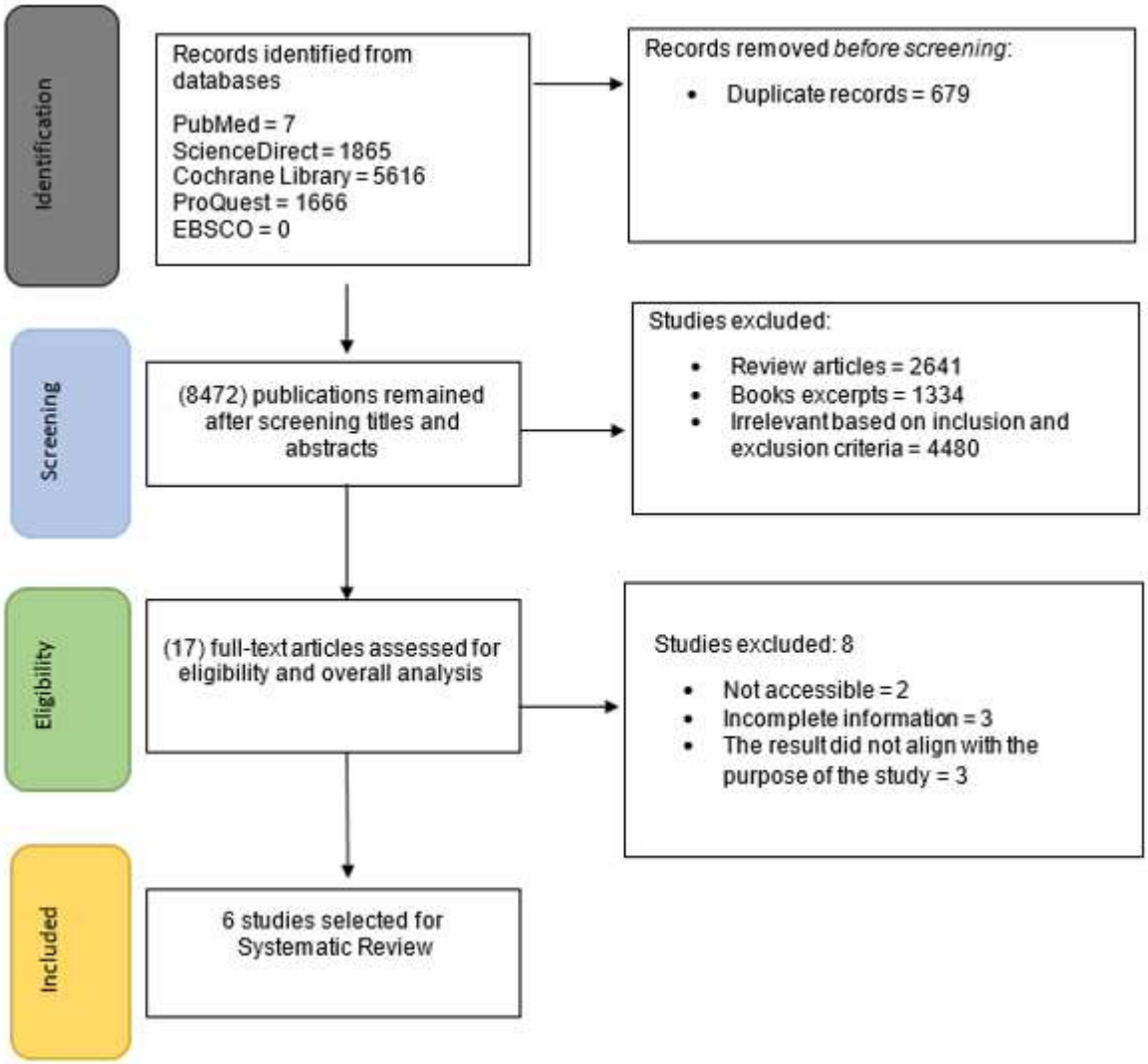


Figure 1: PRISMA Framework.

Demography and Clinical Characteristics of the Included Studies

Each study's demography and clinical characteristics were examined and listed in **Table 2.** Of the six included studies, LAmB or Amphotericin B plus Caspofungin and LAmB or Amphotericin B plus azole combination were included in 4 studies. Only 1 study included the use of caspofungin in combination with azole antifungal. The use of antifungal as monotherapy was analyzed in 3 of the studies, whereas three other studies focused on combination antifungal therapy. The outcomes of these studies also vary, with three studies reporting favorable/unfavorable response rates and two reporting complete response rate (CR) and overall response rate (OR). 2 studies reported mortality rate. In contrast, 1 reported overall and 100-day survival rates as an outcome.

Table 2: Characteristics of Studies.

Author, Year	Country	Participants	Age (Mean±SD or Median (Range))	Included fungal infection in the study and the diagnostic method used	Intervention (n)	Primary Outcome
Yüksek et al, 2023	Turkey	28 children (33 episodes)	8.79 years ±5.03	Mixed IFI (not specified) in hematologic malignancies	LAmB plus Caspofungin (4) LAmB plus Voriconazole (18) Voriconazole plus Caspofungin (10) LAmB plus Posaconazole (1)	Complete Response (CR), Overall Response (OR)
Meena et al, 2019	India	14 children	8.5 years (2.4-14.4)	IFI as diagnosed based on EORTC/MSG Consensus	AmB plus Voriconazole (10) AmB plus Caspofungin (4)	Favorable/Unfavorable response
Lee et al, 2017	Korea	22 children	6.99±4.20	IFI in acute leukemia as diagnosed based on EORTC/MSG Consensus	CAmB (4) LAmB (7) CAmB plus LAmB (9) CAmB plus LAmB plus Fluconazole (1)	OR, CR, Partial response (PR), death
Yilmaz et al, 2011	Turkey	17 children (19 episodes)	63 months (6 months–17 years)	Refractory IFI, as diagnosed based on EORTC/MSG Consensus and the Platelia *Aspergillus* enzyme-linked immunoassay to detect galactomannan antigen	Monotherapy with LAmB (17) Combination of LAmB + Vaspofungin (11) Combination Caspofungin + Voriconazole (12) Monotherapy with Voriconazole (7) Monotherapy with Caspofungin (11) Total LAmB (17) Total Caspofungin (17) Total Voriconazole (14)	mortality rates, responses (favorable/non-favorable), overall complete resolution
Burgos et al, 2008	USA	139 episodes	10.1 years (17 days – 18 years)	IFI in patients who have undergone hematopoietic stem cell transplant, including *Aspergillus fumigatus, A. flavus, A. terreus, A. niger, and other Aspergillosis*. IFI was diagnosed based on EORTC/MSG Consensus, *Aspergillus* culture and immunoassay.	Monotherapy (27) 2 antifungal agents (44) ≥ 3 antifungal agents (60)	mortality rates
Cesaro et al, 2007	Italy	40 children	11.05 years (1.18-17.9)	Invasive Aspergillosis in patients who have undergone hematopoietic stem cell transplant. Invasive Aspergillosis was diagnosed based on microbiological assay and EORTC/MSG Consensus.	Caspofungin and LAmB (18) Caspofungin and Voriconazole (9) Caspofungin and LAmB and Voriconazole (9)	overall survival, 100-days survival favorable unfavourable response

Abbreviation: *AmB, Amphotericin B; CAmB: Conventional Amphotericin B; EORTC/MSG, European Organisation for Research and Treatment of cancer/Mycosis study group; IFI, invasive fungal infection; LAmB, Liposomal Amphotericin B.*

Quality Appraisal

The six included studies were non-randomized; hence, the ROBINS-I tool was used to assess the risk of bias. The overall assessment for all studies shows they were at low risk of bias, except one revealed a moderate risk. The overall risk of bias, as shown in the summary plot, is reported to be about 85% on low risk, which shows that most of the included studies are of good quality **(Figure 2).**

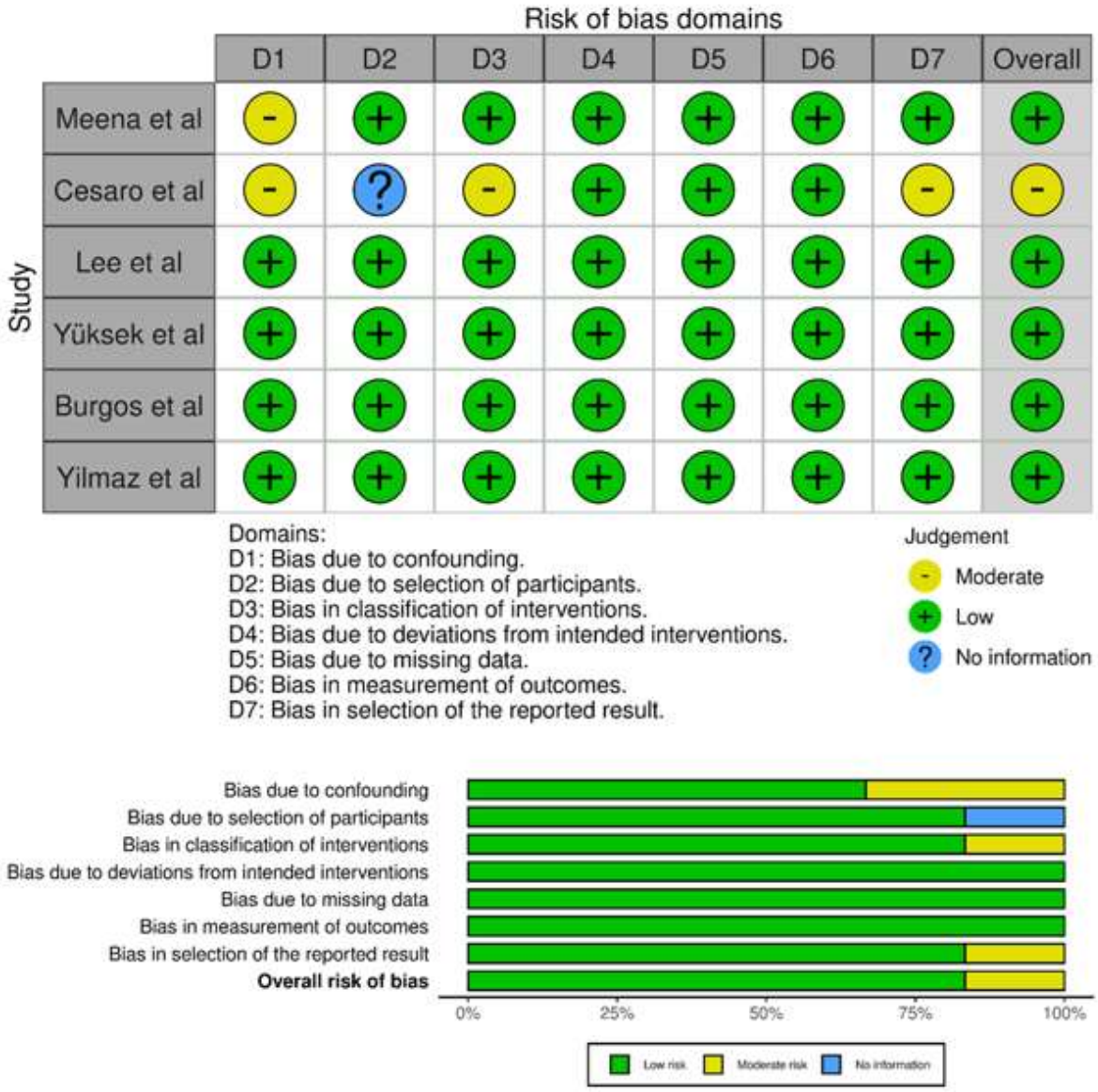


Figure 2: Risk of bias assessment of included studies.

Meta-Analysis of Renal Prophylaxis on Survival Rate

The total number of studies included in this meta-analysis is six, and all reported the survival rates with a total sample size of 160 for the combined antifungal group and 107 for the single antifungal/Placebo group. As seen in Fig. 3, the results showed a statistically significant overall result favoring the combined group with an OR of 0.54 [95% CI 0.29; 1.01, P=0.05]. Heterogeneity was found to be very low and not significant (I2=17%, P=0.31). The funnel plot, as seen in Fig. 3B, Shows no evidence of true heterogeneity among the studies.

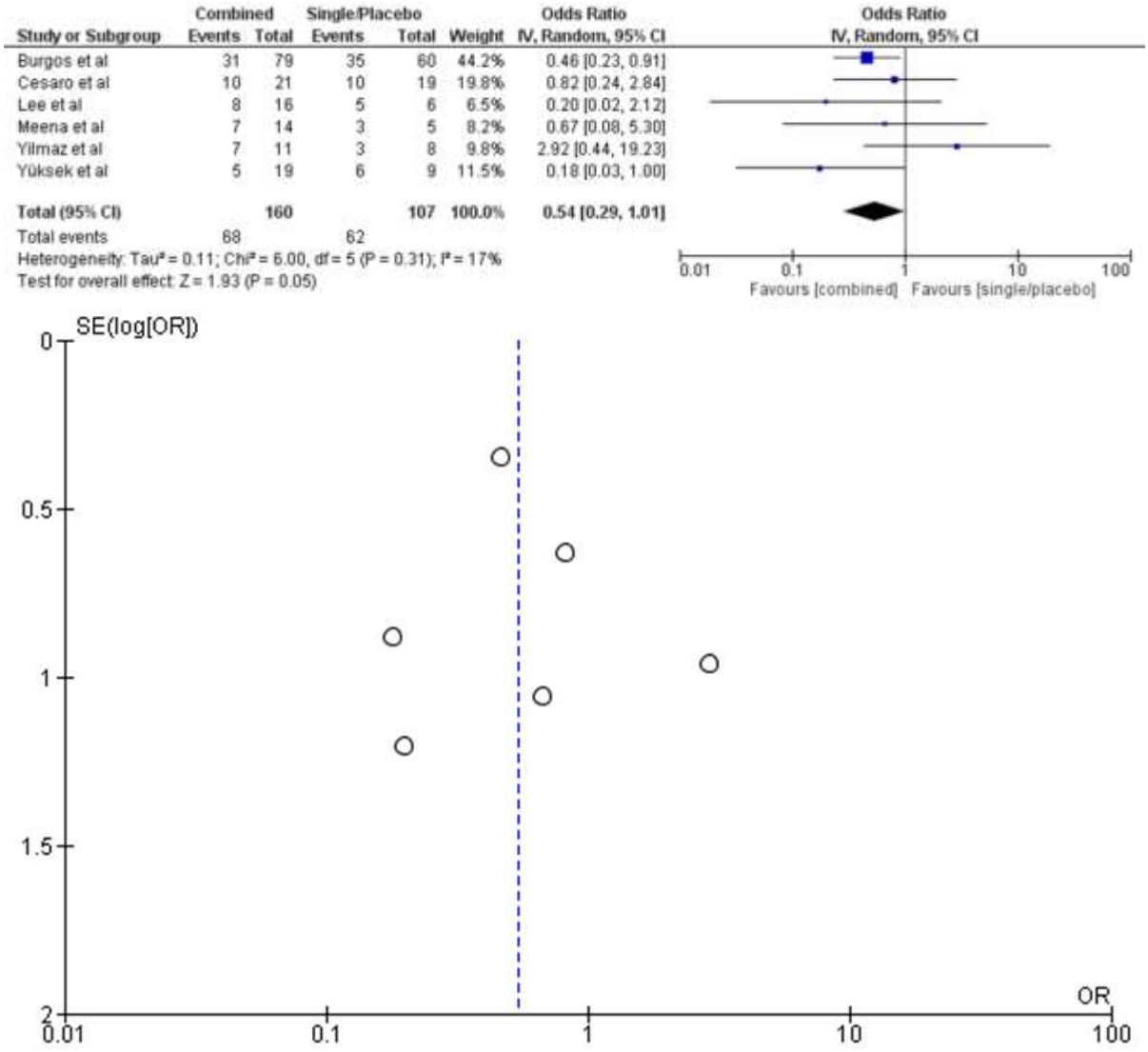
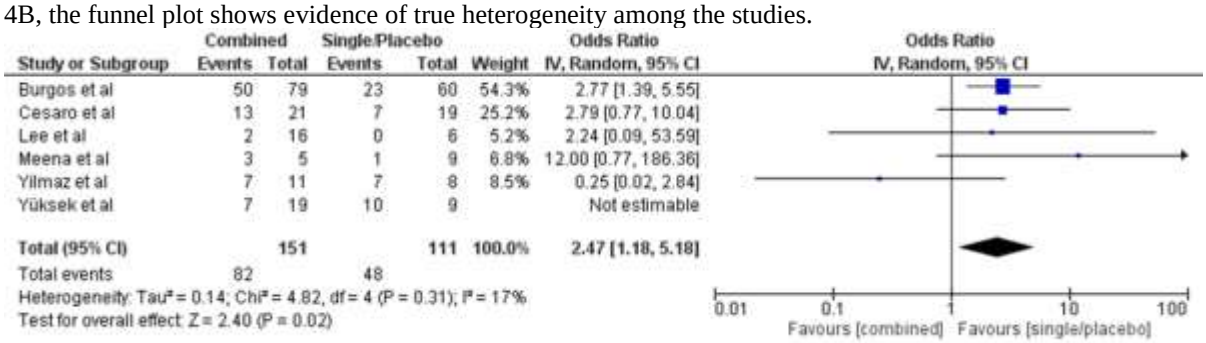


Figure 3: Analysis of the effect of Combination Antifungals on Survival Rate in Pediatric Patients. A. Forest Plot of Renal Prophylaxis on Survival Rate. B. Funnel Plot of Renal Prophylaxis on Survival Rate.

The Effect of Combination Antifungals on Mortality Rate in Paediatric Patients

Six studies also reported mortality rates with a total sample size of 151 for the combined antifungal group and 111 in the single antifungal/Placebo group. The results showed that the single/placebo group has a statistically significant higher mortality rate compared to the combined antifungal group with OR of 2.47 [95% CI 1.18; 5.18, P=0.02 (**Fig. 4A)**. Heterogeneity was found to be very low and not significant (I2=17%, P=0.31). As seen in Fig. 4B, the funnel plot shows evidence of true heterogeneity among the studies.



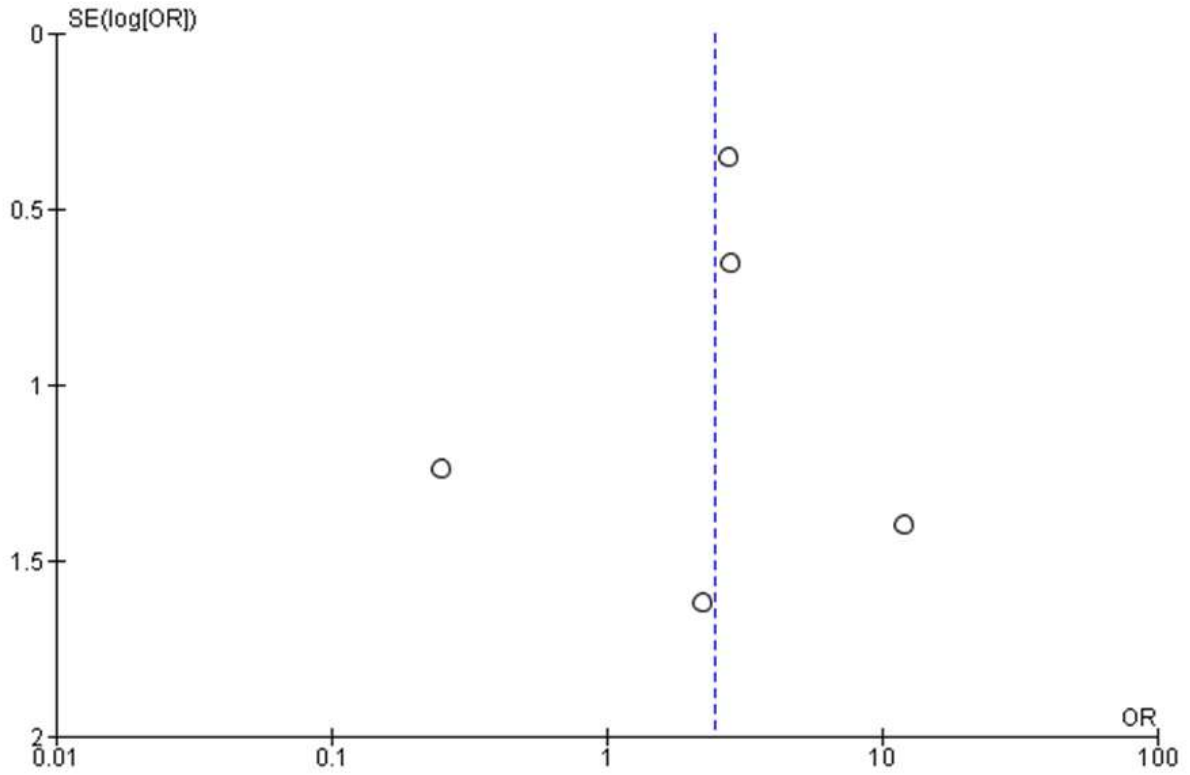
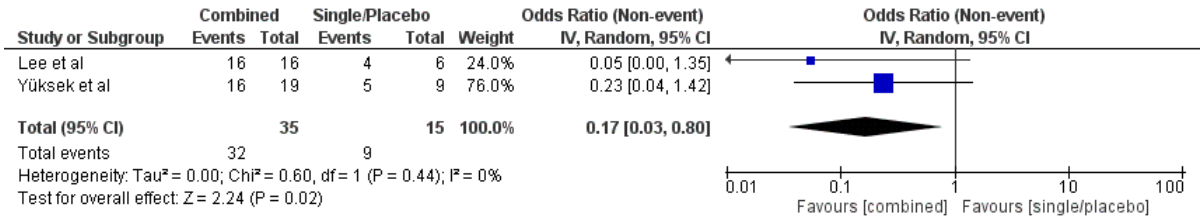


Figure 4: Analysis of the effect of Combination Antifungals on Mortality Rate in Pediatric Patients. A. Forest Plot of Renal Prophylaxis on Mortality Rate. B. Funnel Plot of Renal Prophylaxis on Mortality Rate.

The Effect of Combination Antifungals on Overall Response Rate in Paediatric Patients

Two studies reported the overall response rates with a total sample size of 35 for the combined antifungal group and 15 for the single antifungal/Placebo group. The results showed a statistically significant higher overall response rate in the combined group compared with the single/placebo group with OR of 0.17 [95% CI 0.03; 0.80, P=0.02. Heterogeneity was found to be absent and not significant (I2=0%, P=0.44). The funnel plot in **Fig. 5.** shows no evidence of true heterogeneity among the studies.



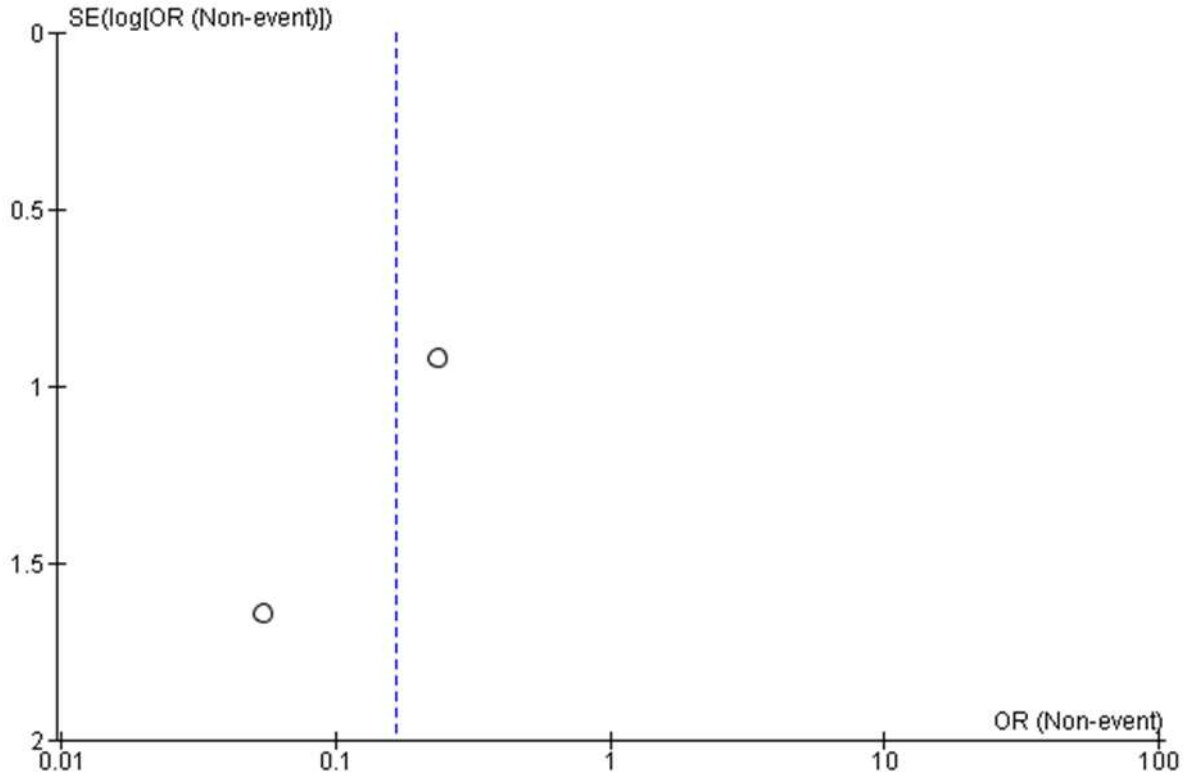


Figure 5: Analysis of the effect of Combination Antifungals on Overall Response Rate in Pediatric Patients. A. Forest Plot of Renal Prophylaxis on Overall Response Rate. B. Funnel Plot of Renal Prophylaxis on Overall Response Rate.

The Effect of Combination Antifungals on Complete Response Rate in Paediatric Patients

Three studies reported the complete response rates with a total sample size of 46 for the combined antifungal group and 23 for the single antifungal/Placebo group. The results showed a non-statistically significant higher complete response rate in the combined group compared to the single/placebo group with of 0.62 [95% CI 0.20; 1.96, P=0.42. Heterogeneity was found to be absent and not significant (I2=0%, P=0.85). The funnel plot, as seen in **Fig. 6**. Shows no evidence of true heterogeneity among the studies.

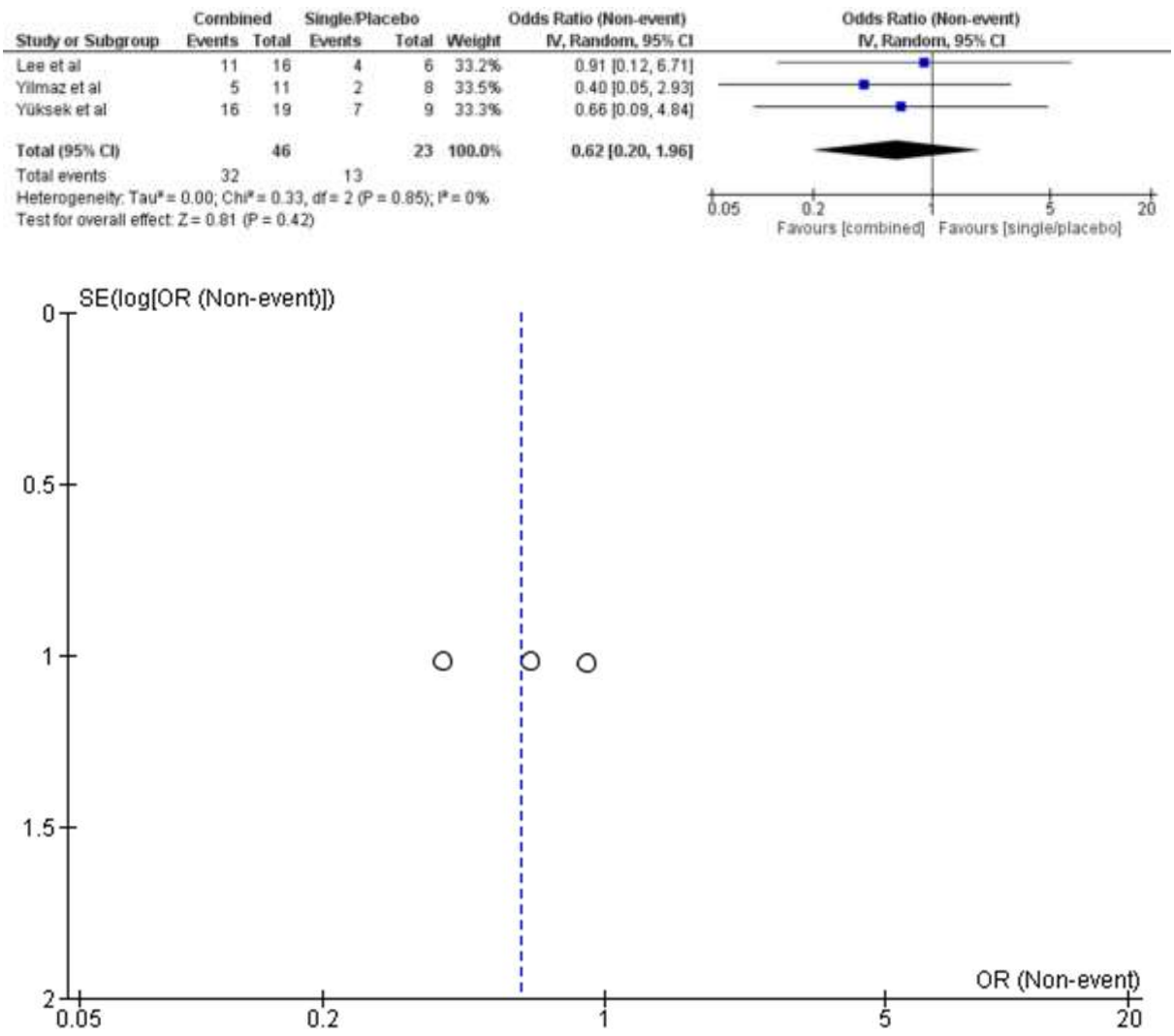


Figure 6: Analysis of the effect of Combination Antifungals on Complete Response Rate in Pediatric Patients. A. Forest Plot of Renal Prophylaxis on Complete Response Rate, panel. B. Funnel Plot of Renal Prophylaxis on Complete Response Rate.

The Effect of Combination Antifungals on Favorable Response Rate in Paediatric Patients

Three studies reported favorable response rates with a total sample size of 37 for the combined antifungal group and 36 for the single antifungal/Placebo group. A non-statistically significant result was found, with the combined group showing a higher favorable response rate than the single/placebo with OR of 0.81 [95% CI 0.18; 3.55, P=0.78]. Heterogeneity was found to be low and not significant (I2=32%, P=0.23). The funnel plot, as seen in **Fig. 7.** shows evidence of true heterogeneity among the studies.

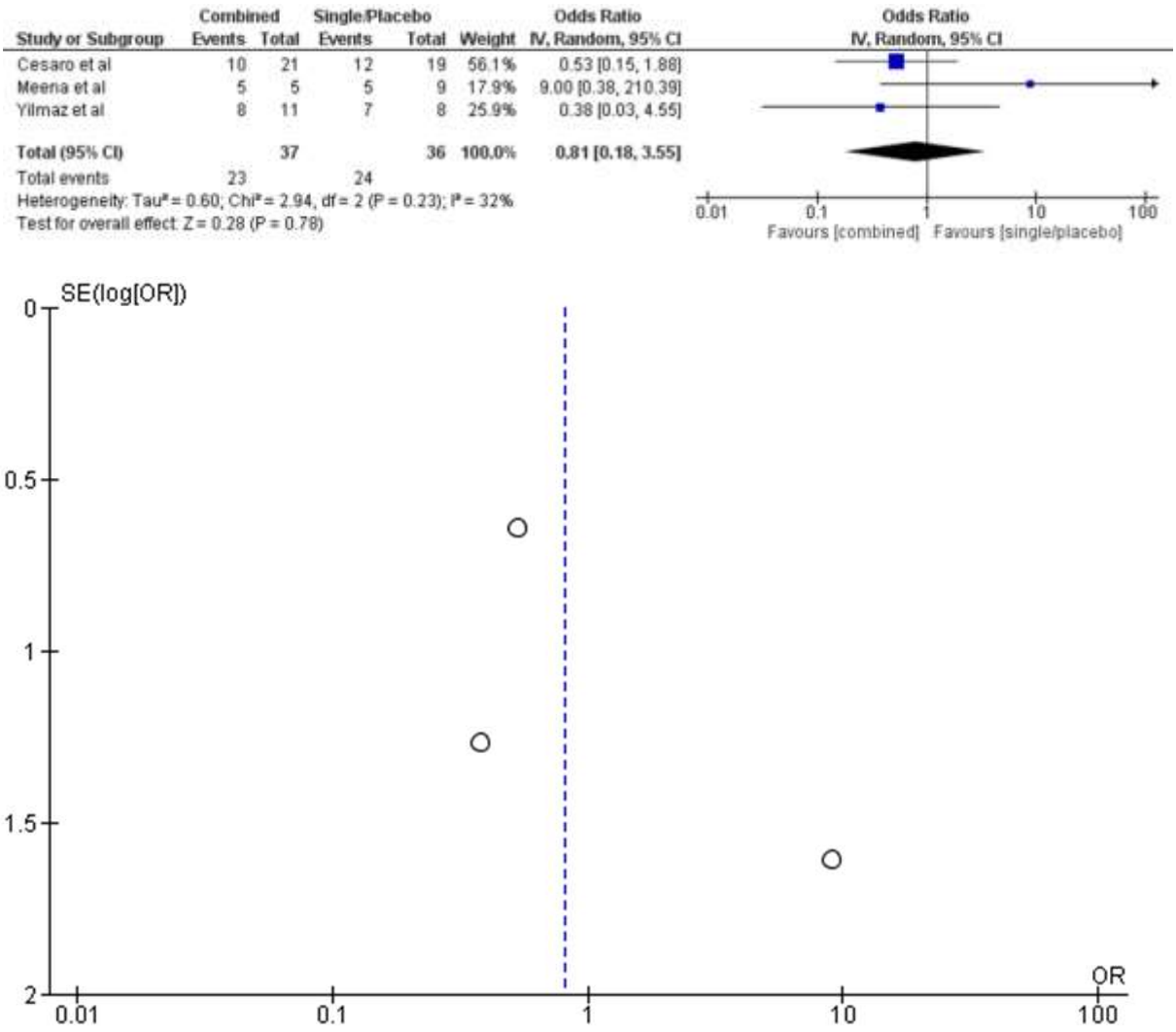


Figure 7: Analysis of the effect of Combination Antifungals on Favourable Response Rate in Pediatric Patients. A. Forest Plot of Renal Prophylaxis on Favourable Response Rate. B. Funnel Plot of Renal Prophylaxis on Favourable Response Rate.

The Effect of Combination Antifungals on Unfavorable Response Rate in Paediatric Patients

Only one study reported unfavorable response rates, with a total sample size of 5 for the combined antifungal group and 9 for the single antifungal/Placebo group. The results showed a non-statistically significant higher unfavorable response rate in the single/placebo compared to the combined group with an OR of 2.33 [95% CI 0.22; 25.24, P=0.49]. Heterogeneity was not applicable due to the presence of one study.

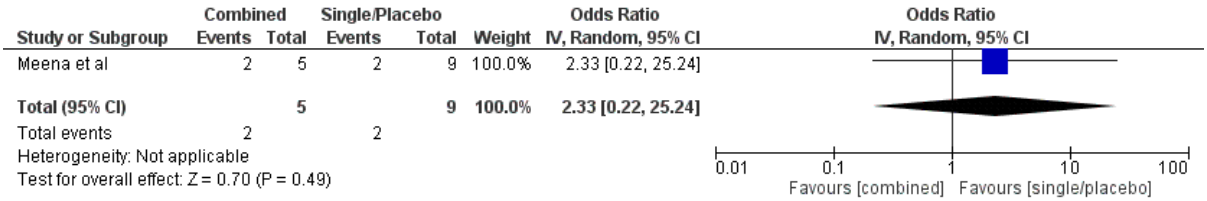


Figure 8: Forest plot of renal prophylaxis on unfavorable response rates.

Discussion

Regarding antifungal therapy in pediatrics, the predominant approach centers around Liposomal-Amphoteriin B (L-AmB), followed by fluconazole and voriconazole.[14] Particularly for high-risk pediatric cases, L-AmB continues to stand out as the primary drug of choice, accounting for nearly 45% of such cases. Additionally, echinocandins, compared to azoles, have demonstrated superior efficacy. Studies regarding antifungal combinations (AFCs) have yet to be explored enough in clinical settings and may increase the risk of drug interactions with little to no difference in efficacy.[15] Nevertheless, in high-risk scenarios such as acute leukemia and allogeneic hematopoietic stem cell transplant (also HSCT), AFCs hold promise due to the generally grim outcomes associated with these cases.[16]

Two commonly studied AFC options include caspofungin with azoles or polyenes. These combinations are favored for their well-tolerated nature and minimal drug interaction profiles. A study reported an overall favorable response rate of 55% with AFCs in high-risk patients with invasive fungal infections (IFIs).[17] Additionally, micafungin has been explored in combination with various antifungal agents, including L-AmB, voriconazole, posaconazole, or caspofungin, yielding an overall response rate of 45% across the entire population—however, specifics regarding the pediatric cohort needed to be delineated.[18] Voriconazole with L-AmB combination therapy has also been reported in patients with aggressive IFI, such as scedosporiosis.[19] Another study reported several combination patterns of AmB with other drugs, including itraconazole, ketoconazole, and flucytosine. The AFCs result in higher survivability, although several risk factors are still associated with a higher risk of death.[20]

Mortality Rate

The utilization of AFCs aims to enhance outcomes in invasive fungal infections (IFIs) among high-risk patients, given the typically poor prognoses associated with such cases. Risk factors for IFIs encompass neutropenia, malignancy, co-infection, antibiotic usage, and central venous catheters.[21] These conditions, by themselves, ultimately increase the mortality rate of IFIs in pediatric patients. From an alternating standpoint, a study has found that IFIs increase the mortality of pediatric patients in immunocompromised states by 20%.[22] Peri et al. demonstrated that half of the mortality causes in these patients are attributable to IFI rather than disease progression.[23] In line with our findings, other studies have also successfully documented a decrease in the mortality rate of patients with AFCs compared to single/placebo groups. One study reported that the mortality rate in 13 children with combination therapy of L-AmB with caspofungin, voriconazole, and posaconazole is 30,7%.[23] In contrast, several other studies employing monotherapy regimens have demonstrated mortality rates of up to 52.5%.[23] These findings have led to promising hope for using AFCs in pediatric patients with high-risk IFIs to lower the mortality rate in most cases.

Survival Rate

Studies have reported the 100-day survival rate of several agents used as monotherapy, including L-AmB (42%),[24] voriconazole (39%),[25] and caspofungin (45%). These figures pale in comparison to the 100-day survival rates achieved with AFCs. Even though our study shows a non-statistically significant increase in survival rate, several other studies have demonstrated the superiority of AFCs in survival rate. One study demonstrated a 70% 100-day survival rate in pediatric patients with high-risk IFIs.[20] In extreme cases of allo-HSCT, IFIs are unfortunately associated with a very low 4-month survival rate of 34%.[26] A study conducted by Marr et al. shows an improved 3-month survival rate in allo-HSCT patients with IFIs compared to the use of voriconazole by itself.[27] These noteworthy findings underline the importance of AFCs as a better alternative strategy to heighten the survival rate when dealing with high-risk IFIs in pediatric patients.

Overall Responses

The overall responses reflect the percentage of patients who have shown a favorable response to the therapy, whether a complete or partial response. Based on the study by Lee et al.,[28] 20 patients out of 22 patients responded to the application of voriconazole and caspofungin combination, in addition to the initial therapy of antifungal monotherapy, indicating a 90.9% overall response rate for the first 100 days of treatment. On the other hand, the study by Yüksek et al.[29] found that the overall response to implementing Combination antifungal therapy, consisting of caspofungin and voriconazole, reached 50%. This result may occur because pediatric patients enrolled in this study have a poor prognosis, such as prolonged neutropenia and relapsed leukemia. These studies' findings can be considered promising and may provide a positive outlook on applying combined antifungals to IFI.

Benefits and implication

The combination of antifungal therapy for treating pediatric patients with IFI has proven to have a positive effect and optimize patients' prognosis compared to using a single antifungal agent alone. Future guidelines regarding combination antifungal therapy need to be established to address the proper use, dosage, and types of drugs that should be combined. Future research can also explore using novel compounds to treat IFI in the pediatric population.[30]

Conclusion

IFI has been noted as a prominent contributor to higher mortality and morbidity rates among pediatric patients with hematological malignancies. This systematic review and meta-analysis have shown that antifungal combination therapy has demonstrated significant efficacy in overall response, favoring combination antifungal therapy. These findings may provide a consideration for exploring the possibility of using combined antifungals to treat IFI. However, future clinical trials are still needed to investigate the effect of combined antifungals on the complete response rate and unfavorable response rate among IFI pediatric patients.

Disclosure

All authors have nothing to disclose.

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